

EXPERIMENTAL REPORTS

MINI-REVIEW

Task-Related Gamma-Band Dynamics From an Intracerebral Perspective: Review and Implications for Surface EEG and MEG

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Abstract: Although non-invasive techniques provide functional activation maps at ever-growing spatio-temporal precision, invasive recordings offer a unique opportunity for direct investigations of the fine-scale properties of neural mechanisms in focal neuronal populations. In this review we provide an overview of the field of intracranial Electroencephalography (iEEG) and discuss its strengths and limitations and its relationship to non-invasive brain mapping techniques. We discuss the characteristics of invasive data acquired from implanted epilepsy patients using stereotactic-electroencephalography (SEEG) and electrocorticography (ECoG) and the use of spectral analysis to reveal task-related modulations in multiple frequency components. Increasing evidence suggests that gamma-band activity (>40 Hz) might be a particularly efficient index for functional mapping. Moreover, the detection of high gamma activity may play a crucial role in bridging the gap between electrophysiology and functional imaging studies as well as in linking animal and human data. The present review also describes recent advances in real-time invasive detection of oscillatory modulations (including gamma activity) in humans. Furthermore, the implications of intracerebral findings on future non-invasive studies are discussed. *Hum Brain Mapp* 30:1758–1771, 2009. © 2009 Wiley-Liss, Inc.

Key words: stereotactic electroencephalography (SEEG); electrocorticography (ECoG); oscillations; gamma-band activity; real-time electrophysiology; functional mapping; invasive human recordings; epilepsy

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INTRODUCTION

Shortly after Berger [1929] reported the first electroencephalography (EEG) measurements in humans using electrodes placed on the scalp the technique was adapted by neurosurgeons to directly acquire intracerebral signals from patients. Such recordings proved to be of great interest for pre-surgical brain mapping allowing for clinical assessments with an unprecedented spatial precision [Jasper and Penfield, 1949; Ward and Thomas, 1955]. These early studies marked the birth of a new field that would

expand beyond its clinical application to the field of brain research. Indeed, more than fifty years later, intracranial electroencephalography (iEEG) has become an essential component of the pre-surgical routine procedures for a wide range of neurological diseases including drug-resistant epilepsy, Parkinson disease, essential tremor, brain tumors, while providing unique insights into brain function [Engel et al., 2005]. Early observations that changes in iEEG recordings were correlated with the patient's environment or behavior [Jasper and Penfield, 1949] gradually laid the foundations for a new research field bringing together clinicians and neuroscientists and advancing our understanding of the neural mechanisms underlying human cognition. Despite a number of restrictions inherent to the therapeutic context of its application, iEEG has grown into a field of its own, yielding a steady stream of seminal observations ranging from the functional organization of the human visual system [Allison et al., 1999; Halgren et al., 1994] to response properties of individual neurons during mental imagery in the anterior temporal lobe [Kreiman et al., 2000] to name but a few examples of iEEG's important input to neuroscience.

In this review, we provide a short overview of iEEG and discuss its advantages and its limitations for cognitive neuroscience as well as its relationship to non-invasive brain mapping techniques. A comprehensive review of invasive recordings in a range of clinical conditions including movement disorders such as Parkinson's disease can be found in Engel et al. [2005]. Here, we restrict the discussion to invasive recordings acquired from implanted epilepsy patients either with stereotactic-electroencephalography (SEEG) or electrocorticography (ECoG) and focus on current topics in invasive functional mapping based on the detection of task-related modulations of cortical oscillations. In particular, we discuss the efficiency of detecting gamma-band activity (>40 Hz) using offline and online analysis for invasive functional mapping [Crone et al. 2006; Jensen et al. 2007], and its putative role in bridging the gap between electrophysiology and functional imaging studies as well as linking animal and human data. In addition, we aim to dispel certain misconceptions about the significance and interpretability of human invasive recordings by outlining their unique advantages and explicitly describing their inherent limitations. Finally, we also address the relationship and complementarities between iEEG and non-invasive electrophysiological studies.

INVASIVE RECORDINGS IN EPILEPSY

Intracerebral recordings in humans are performed using a wide range of techniques tailored to the neurological disorder and therapeutic strategy at hand. Depth recordings are for instance used during positioning of a deep brain stimulation (DBS) electrode in Parkinson's disease [Benazzouz et al., 2002; Engel et al., 2005]. Furthermore, invasive recordings are used in patients with intractable

epilepsy in order to simultaneously and chronically probe the neural activity in multiple brain structures during a pre-surgical evaluation period.

The Clinical Setting

In patients with pharmacologically resistant epilepsy, iEEG is used to identify cortical regions critical for seizure onset and identify others that need to be spared at the time of surgery [e.g., Kahane et al., 2004]. The intracerebral electrodes sometimes stay in place for more than two weeks in order to localize the origin of fast electrophysiological rhythms that precede seizure onset and that are at the core of the epileptogenic network. Surgical resection of the focus of the seizure has been shown to yield up to 70% success rates for drug-resistant temporal lobe epilepsy [Engel, 1996]. Intracranial EEG is used to test one or several hypothesis regarding the anatomical organization of the epileptogenic network. This sometimes implies that intra-cerebral electrodes are positioned in widely distributed brain regions that might include pathological but also healthy tissue. Therefore, such a clinical context can also provide a unique opportunity to study fundamental questions about neural coding and cognition. The rest of this review is dedicated to iEEG data acquired in the clinical context of epilepsy.

Stereotactic-EEG and Electrocorticography: Two Intracranial Recording Techniques

Although microelectrodes have been used in humans to acquire single-neuron spiking data [Fried et al., 1997; Heit et al., 1988; Ojemann et al., 2002; Ward and Thomas, 1955], clinical recordings in epilepsy patients are generally performed using macroelectrodes that measure coherent activity of local neuronal populations in the vicinity of the recording site. The most common choice in the clinical routine is to use either stereotactic-electroencephalography (SEEG) or electrocorticography (ECoG) which acquire intracranial data using multilead depth electrodes or subdural grid electrodes respectively (see Fig. 1). Subdural grids consist of 2D arrays (or sometimes one-dimensional strips) of electrodes positioned directly on the lateral surface of the brain, with a typical inter-electrode distance of 1 cm [Engel et al., 2005]. In contrast, depth electrodes are semi-flexible one-dimensional linear arrays, shaped as narrow needles that penetrate deep into the brain. Such depth electrode implantations are often referred to as Stereotactic EEG because a stereotactic technique developed by Talairach and Bancaud is used to localize the electrodes [Kahane et al., 2006]. While subdural grids provide widespread cortical coverage and cortical maps of gyral activity, the multilead depth electrodes record from both sulci and gyri and go beneath the cortical surface to probe deep cortical structures, such as the cingulate gyrus, and occasionally subcortical structures, such as the lateral geniculate nucleus [Krolak-Salmon et al., 2003] or the nucleus

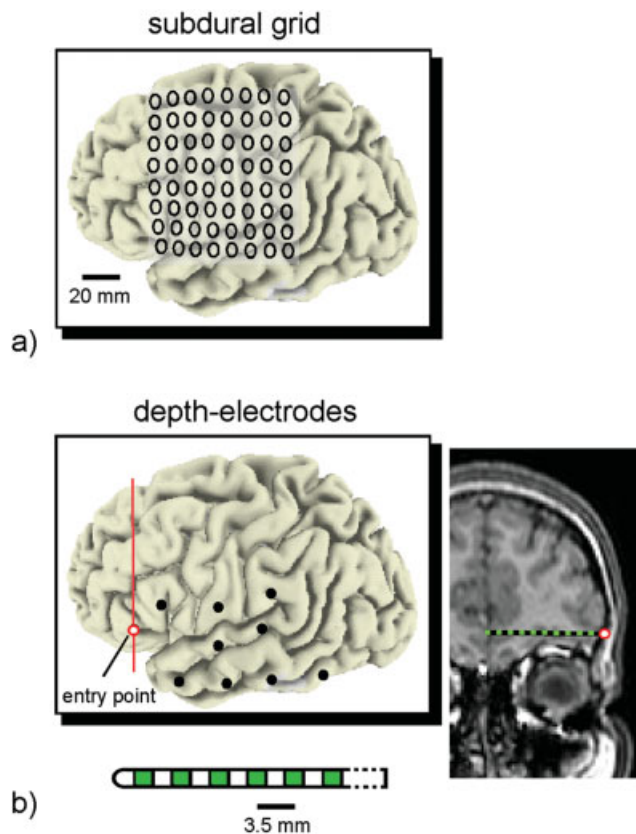


Figure 1.

Subdural grids vs. depth electrodes. (a) Representation of electrocorticographic (ECoG) subdural grid electrodes. Open circles indicate recording sites on a 8-by-8 matrix covering the lateral surface of the somatosensory cortex. (b) Example of implantation with stereotactic encephalography (SEEG) electrodes. Black dots represent the entry points of ten depth electrodes. Each electrode consists of 5–15 contact sites (green squares). In most cases, SEEG electrodes are inserted orthogonal to the inter-hemispheric plane as shown on coronal MRI slice.

acumbens [Munte et al., 2008]. A further difference between SEEG and ECoG is that while depth electrodes require small burr holes for implantation the implantation of two-dimensional subdural grids involves a larger craniotomy.

Converging evidence suggests that both grid [Menon et al., 1996] and depth-electrodes recordings [Lachaux et al., 2003] provide sufficient spatial resolution to localize neural activity at the gyral level, a precision that is as good as, if not better, than what is achieved with fMRI. In addition, the spatial precision of the analysis also depends on the accuracy of electrode localization [Dalal et al., 2008a] and choice of reference electrode. In SEEG data, the local precision is highest when each recording site is referenced to its nearest neighbor (bipolar montage) than when

one remote site is used as reference for all channels (common reference) [Lachaux et al., 2003].

Unless otherwise stated in the manuscript, the experiments performed by our group that are reported in this review were carried out using multi-channel video-EEG acquisition and monitoring system (Micromed, Treviso, Italy) that simultaneously records the intracerebral activity from up to 128 depth-EEG electrodes (up to 1024 Hz sampling rate and a 0.1–200 Hz bandpass filter). As a general rule, twelve to fourteen semi-rigid multi-lead electrodes are stereotactically implanted in each patient. The stereotactic-EEG (SEEG) electrodes used have a diameter of 0.8 mm and, depending on the target structure, consist of 5–18 contact leads 2 mm wide and 1.5 mm apart (Alcys, Besançon, France).

Strengths and Limitations of iEEG Research

At first sight, iEEG can be seen as combining the best of two worlds: the spatial resolution of fMRI and the temporal accuracy of MEG/EEG. In addition, given that the recording sites are within the brain, iEEG signals are immune to a large range of external artifacts (e.g., eye blinks, face and neck muscles contractions). However, it is important to bear in mind two significant limitations: first, the data acquired report on patients with epileptic disorders and, second, the invasive electrodes only provide a limited coverage of the brain.

Indeed, in recent years, iEEG research has begun to establish a set of methods and specific practices to limit the risk of making physiological interpretations based on phenomena that actually reflect the pathological condition of the patients. It is common iEEG practice to discard signal epochs that show any type of epileptiform activity. Furthermore, most iEEG studies include post-surgical information about the spatial organization of the epileptogenic network and do not report on task-related responses within that network. Also, when possible, an additional caution is to only report observations that are reproducible across several patients with different types of epileptogenic networks and anticonvulsant medication [Fell et al., 2002; Halgren et al., 1994]. Nevertheless, an important body of iEEG research provides evidence that such issues can indeed be overcome to an extent that warrants the physiological significance of the physiological insights and novel hypotheses drawn from the data [Axmacher et al., 2008b; Brovelli et al., 2005; Canolty et al., 2006; Crone et al., 1998a, 2006; Fell et al., 2002; Jung et al., 2008; Lachaux et al., 2003, 2005, 2006a; Lakatos et al., 2008; Mainy et al., 2007].

The second limitation of many iEEG investigations is the fact that the electrode implantation scheme only provides a restricted sampling of selected cerebral structures. A complete 3D coverage of the brain with a spatial resolution of 3.5 mm has been estimated to require about 10,000 recording sites [Halgren et al., 1998], that is roughly 100 times more than the number of sites we actually record (approx. 100). A more comprehensive view of the large-

scale networks involved in various cognitive tasks would therefore require combining data from multiple subjects with both overlapping and complementary electrode positions. In practice, collecting data from comparable anatomical origin across several patients is of non-negligible difficulty since the target structures for intracerebral electrodes placement is determined in each patient individually and independently of research objectives. The standards of invasive and non-invasive research are thus inherently different. Furthermore, to a certain extent, iEEG studies share some common aspects with monkey electrophysiology studies. The latter report in most cases on two or three animals with recordings in comparable regions and with a particularly high signal-to-noise ratio. In addition, the limited extent of probed cerebral structures (spatial coverage) and the question of generalization to the healthy human brain are undoubtedly two issues that are also relevant to findings reported invasively in monkey studies. Animal studies provide valuable observations and hypotheses that ultimately need to be explored and validated in humans. Similarly, the results of iEEG studies in human patients may be further validated in healthy subject by non-invasive techniques such as MEG and EEG.

SPECTRAL COMPONENTS OF iEEG DATA

Oscillatory brain responses are not perfectly phase-locked with respect to experimental stimuli and are thus discarded by the time-domain averaging of the data typically used to compute event-related potentials (ERPs). Therefore, with the advent of enhanced computing power, novel time-frequency domain approaches were applied to assess such activations, described as *induced responses*, by contrast to the phase-locked activations known as *evoked responses* [Tallon-Baudry and Bertrand, 1999]. As an example, using time-frequency analysis intracranial data in humans have reported that motor behavior is associated with spatially focal increases in high frequency (>40 Hz) activity and widespread decreases in lower frequencies (8–30 Hz) in the motor cortex [Aoki et al., 1999; Crone et al., 1998a; Lachaux et al., 2006a; Mehring et al., 2004; Pfurtscheller et al., 2003; Pistohl et al., 2008; Szurhaj et al., 2005].

Gamma-Band Activity Modulations: A Robust Correlate of Local Neural Activation

Several early animal microelectrode studies pointed towards the putative functional importance of synchronized neural oscillations at high frequencies (>40 Hz), i.e., within the gamma band [Eckhorn et al., 1988; Freeman, 1978; Gray et al., 1989; Rougeul-Buser et al., 1975]. Neural synchronization in the gamma band has been proposed as a fundamental mechanism for neural communication underlying both perceptual and motor processes [Murthy and Fetz, 1992; Singer and Gray, 1995]. In addition, several scalp EEG studies reported task-related responses in the

gamma band in a variety of visual paradigms [Gruber et al., 1999; Tallon-Baudry et al., 1996] suggesting a link to the neural synchronization phenomenon recorded invasively in animals.

Forty years after Chatrian's seminal report [Chatrian et al., 1960], task-related gamma band increases were observed in direct recordings of the human brain using tightly controlled experimental paradigms and advanced signal processing analysis [Crone et al., 1998a; Lachaux et al., 2000]. Ever since, an increasing number of iEEG studies in humans (epilepsy patients for the large part) report gamma-range activations in various brain structures and in various experimental conditions. Interestingly, although research into the functional significance of gamma activity is still in its early days, converging findings from these studies point to a number of properties of gamma-band responses (GBRs) that appear to be reproducible across a variety of brain structures and in various experimental conditions. Previous work including numerous ECoG and SEEG studies by our group and others suggest that these common characteristics could be tentatively summarized as follows:

1. Broad frequency extent: gamma-band responses (GBR) consist of spectral power increases (or suppressions) that are time-locked to sensory or motor events, in a broad range of frequencies (40–200 Hz). Note also that task-related gamma-band suppressions (GBS) have recently been reported with iEEG [Lachaux et al., 2008].
2. Functional specificity: the fine spatial organization of GBRs strongly depends on the cognitive process at hand. For example, Figure 2 illustrates this specificity within Broca's area during a word recognition task (semantic versus phonological processing). Similarly, we have also reported using SEEG in an implanted subject performing an auditory experiment, that switching the auditory stimulus from speech to music causes a seven millimeters shift in the focus of the GBR locus in the Superior temporal gyrus [Lachaux et al., 2007a].
3. Spatial specificity: Although sources of GBRs have been found across distributed brain areas, each GBR source per se generally shows spatially focal activation. This contrasts with the wider spatial distribution of power modulations in lower frequency bands such as the alpha (8–13 Hz) or beta (15–30 Hz) bands. This general observation has been shown to be particularly clear in the sensorimotor cortex [Crone et al., 1998b], but is also visible during visual search tasks for instance (cf. Fig. 3).
4. Generalization: large-scale networks exhibiting GBRs have been found in a large variety of cognitive tasks involving working memory [Axmacher et al., 2008b; Howard et al., 2003; Mainy et al., 2008], declarative memory [Axmacher et al., 2008a; Fell et al., 2001, 2002, 2008; Sederberg et al., 2007], reading [Mainy

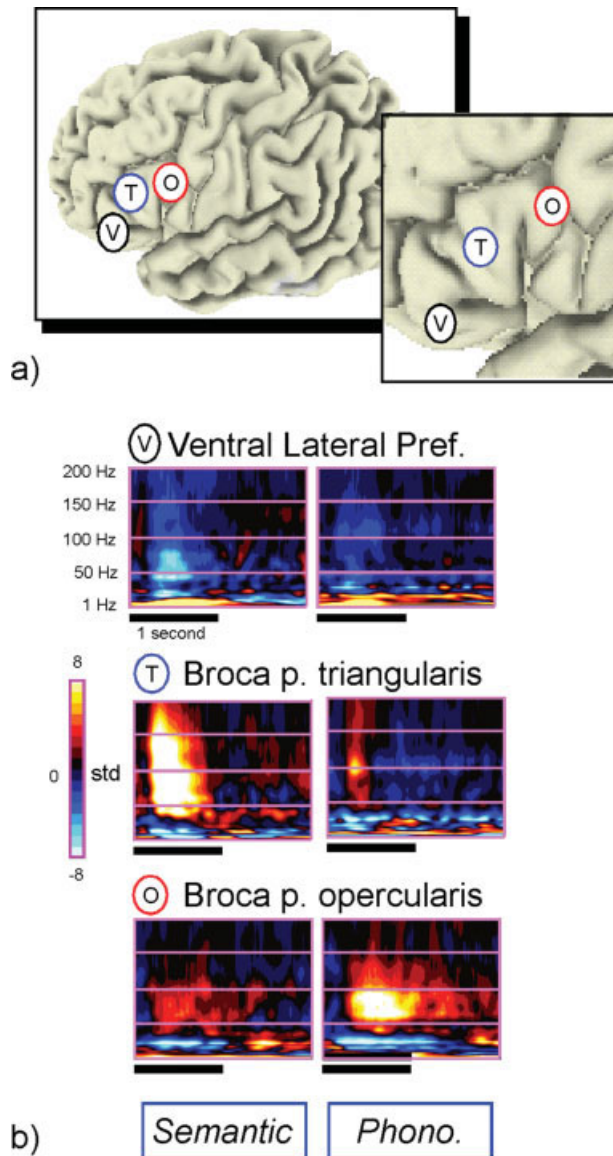


Figure 2.

Illustration of the functional specificity of gamma-band activity in a word recognition task. Patients had to perform either an animacy decision on written words (Semantic task) or rhyme detection on visually presented pseudo-words (Phonological task). Time-frequency (TF) representations show energy increases and decreases relative to pre-stimulus baseline across the two conditions in three distinct regions: Broca pars triangularis ('T'), Broca pars opercularis ('O') and Ventral Lateral Prefrontal Cortex ('V') (response is shown for 2 seconds after stimulus onset). Energy increases above 50 Hz clearly differentiate between task conditions in Broca ('T' and 'O'). Enhanced gamma-band responses in Broca coincide with gamma-band suppression in the VLPFC (V). TF maps also display a clear Broca power suppression in all conditions below 30 Hz, i.e., in the alpha and beta bands.

et al., 2008], speech perception and production [Crone et al., 2001b], attention [Brovelli et al., 2005; Jensen et al., 2007; Jung et al., 2008; Ray et al., 2008], visual [Lachaux et al., 2005; Tanji et al., 2005], auditory [Bidet-Caulet and Bertrand, 2005; Crone et al., 2001a; Edwards et al., 2005], somatosensory [Aoki et al., 1999] and olfactory perception [Jung et al., 2006], motor processes [Crone et al., 1998a; Lachaux et al., 2006].

Although the above properties should by no means convey the impression that GBRs provide by themselves a comprehensive view of task-related neural dynamics, they do highlight, in our opinion, the importance of exploring the functional significance of gamma range activity. Whether GBRs represent a phenomenon that is intrinsic to cognition is still debated. A theoretical framework which draws upon single-unit recordings in animal studies suggests that gamma-band synchronization facilitates neural communication [Fries, 2005; Singer, 1999]. Compared to a resting baseline level, gamma-band activity recorded within a neural population would increase when its neurons are recruited by a cognitive process, and conversely, gamma power might be expected to decrease when the population is no longer necessary or when its activity is inhibited [Lachaux et al., 2008]. The view that engagement in a cognitive act triggers a large-scale network of distributed and spatially focal enhancements and suppressions (i.e., positive and negative modulations) of gamma-band responses compared to the resting state provides an attractive framework for comparison with fMRI studies. Indeed, recent studies both in animals and in humans report prominent spatial overlap between the networks of gamma-band activations and those of the BOLD signal suggesting a direct relationship between the two [Kayser et al., 2004; Lachaux et al., 2007b; Logothetis et al., 2001; Niessing et al., 2005; Nishida et al., 2008].

Oscillatory Modulations in Lower Frequency Bands

In addition to GBRs, time-frequency analysis of iEEG data has also revealed robust task-related response patterns in lower frequency bands, mostly in the theta (4–7 Hz), alpha (7–14 Hz) and beta (15–30 Hz) bands. Results obtained with iEEG are largely in line with reports from scalp recordings, and often reveal alpha and beta power suppressions during the task compared to the baseline period. For instance, such findings were reported in the sensori-motor cortex and described as event-related mu and beta desynchronization [Crone et al., 1998b; Pfurtscheller et al., 2003] as well as in the parieto-occipital cortex [e.g., Adrian, 1941]. Furthermore, alpha and beta suppressions often occur simultaneously with GBRs. Although there has been, to our knowledge, no extensive iEEG data meta-analysis that specifically explores this relationship, it has often been reported in humans with iEEG studies [Crone et al., 1998a,b; Lachaux et al., 2005] and MEG recordings [de Lange et al., 2008] as well as in animal studies [e.g., Rickert

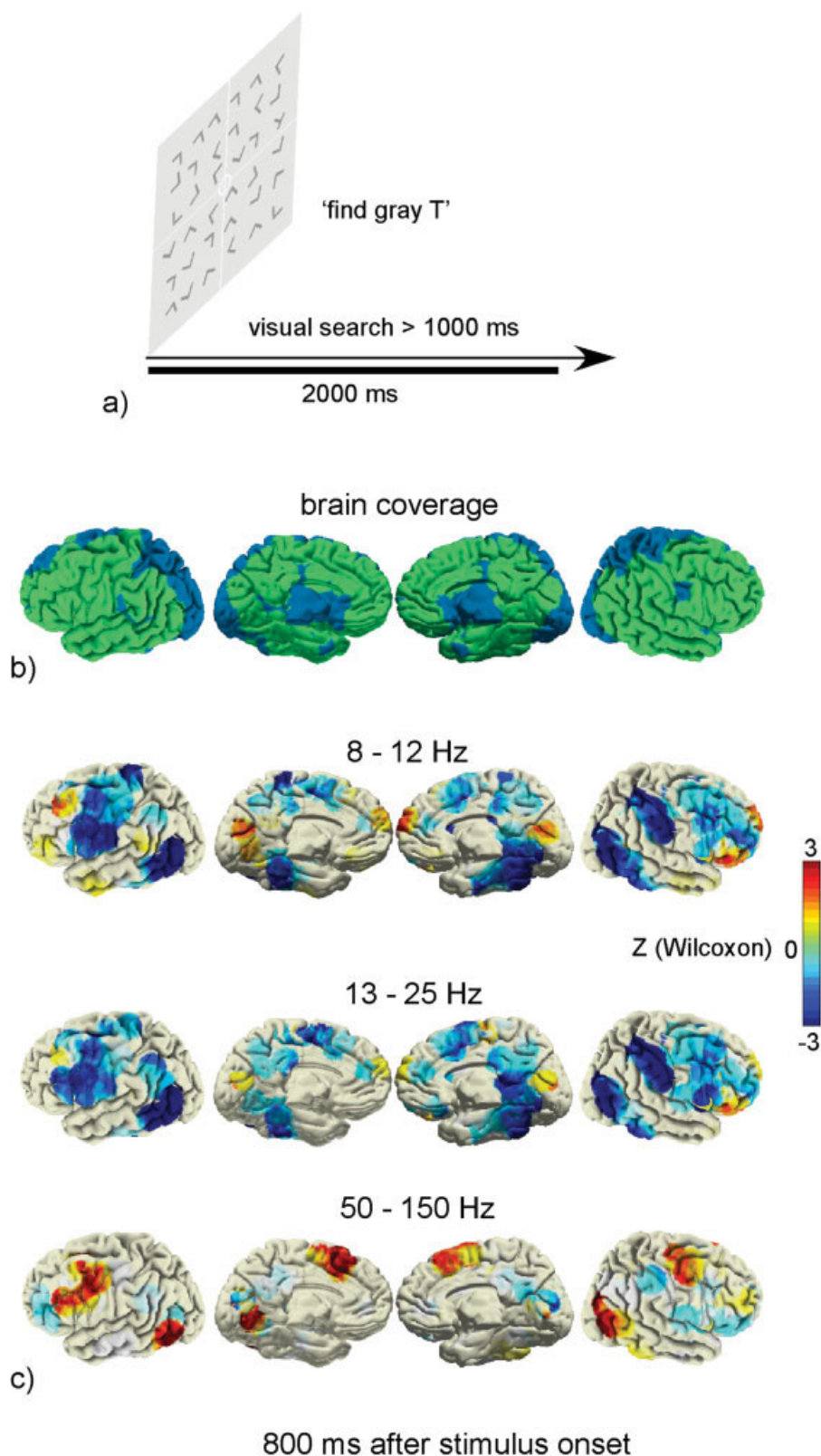


Figure 3.

The spatial distribution of alpha, beta, and gamma-band responses during a visual search task. (a) Paradigm: The patients were asked to search for a gray 'T' within an array of distracters (gray 'L's'). (b) Cortical areas within direct vicinity of electrode sites across all ten patients (green). (c) Following the same convention as in Supplementary Figure 1b, 3D brain reconstructions show the distribution of alpha (8–12 Hz), beta (13–25 Hz) and gamma (50–150 Hz) responses 800 ms after stimulus onset, i.e., while patients are actively searching for the target. Response is expressed in energy variation relative to pre-stimulus baseline (Wilcoxon Z score, FDR corrected).

et al., 2005]. Additionally, alpha and beta desynchronizations have been found to occur across cortical areas that often include, but also extend beyond the origin sites of GBR. Figure 3 shows an illustration of this pattern in a visual search task. This has also been reported in the motor cortex, where the spatial organization of movement-related GBR provides a precise focal spatial mapping, while alpha and beta suppressions yield spatially smoothed maps [Crone et al., 1998a]. As shown in Figure 2, such a reversal between high and low frequency activation patterns is also visible in a word recognition paradigm contrasting semantic and phonological processing [Mainy et al., 2008].

Modulations of theta (4–7 Hz) activity have also been consistently reported in iEEG [Kahana et al., 2001; Raghavachari et al., 2001]. In contrast to alpha and beta activity, and much like the gamma band, theta activity appears to be a rhythm often observed to increase in amplitude during active involvement in a task. For instance, theta power increases have been reported in the hippocampus during spatial navigation [Ekstrom et al., 2005] and with memory load during the delay of a verbal working memory task in multiple frontal, temporal and parietal areas [Raghavachari et al., 2001]. The observation that both gamma and theta power increases during cognitive processing may suggest that the two rhythms interact with each other. Indeed, theta–gamma interactions have been reported in animals and in humans [Canolty et al., 2006; Jensen and Colgin, 2007].

Intracranial Event-Related Potentials

Event-related potentials measured at the intracerebral level have been explored extensively by numerous fundamental iEEG studies. A detailed review of this literature is beyond the scope of this review. Interestingly, however, ERPs and cerebral oscillations are often investigated separately. Only a few studies have sought to establish links between the two [Karakas et al., 2000; Mazaheri and Jensen, 2008; Nikulin et al., 2007]. A handful of studies have compared the task-sensitivity and spatial organization of ERPs and gamma-band responses and revealed a degree of overlap between the two systems. For instance, in a paradigm that required participants to detect faces hidden in high-contrast figures, the presented stimuli triggered both ERPs and gamma-band responses in the same region of the fusiform area [Lachaux et al., 2005]. However, this particular study did also reveal that, on some instances, the ERP was identical whether the face was actually detected or not, while GBR was stronger for detected faces. This is in line with other iEEG results that report functional dissociations between ERPs and gamma-band responses [Tallon-Baudry et al., 2005].

An illustrative iEEG example: ERPs and GBR in early visual areas

In a matched to sample task, subjects were instructed to compare two complex and simultaneously presented stimuli and decide whether they are the same or different. Subjects were allowed to freely explore both stimuli as long as

they wanted before giving a behavioral response. The differences between the stimuli were hard to detect and a decision required multiple saccades back and forth between the two (see Fig. 4a). By contrast to surface recordings, the saccades that precede each fixation on the left or right stimulus did not elicit signal artifacts. A key question in this study was therefore to investigate the neural activity related to fixation (gaze immobilization at the end of each saccade). Visual ERPs and GBRs were obtained from the neural signal acquired in multiple sites in the occipital lobe of two patients.

In order to describe the propagation of neural activity in early visual areas, we considered two electrodes one located in primary visual cortex and the other in latero-occipital area. The first peak latency of the ERPs was identified and used to describe the direction of neural activity propagation. In primary visual area the average latency for each subject was 32 and 29 ms, while in latero-occipital area the average latencies were 165 and 155 ms, for subjects one and two respectively. Time-frequency analysis revealed GBR (50–150 Hz) with onset latency around 38 and 44 ms (Fig. 4c) which were only observed in the primary visual area, not in the lateral-occipital sites (see Fig. 4d).

The ability to align the analysis on the end of a saccade when using direct recordings from the cortex allows for the investigation of brain activity in humans during a free viewing experiment. Our observations suggest that the onset of foveal vision following a saccade to an already existing object elicits ERPs and high gamma responses in primary visual areas. Most interestingly this activity starts earlier than latencies one might have expected from previous reports [Poghosyan and Ioannides, 2007; Schmolesky et al., 1998]. We propose that this probably related to the fact that previous experiments used stimuli that were flashed in the visual fixation point of the subject. Here, stimuli were present on the screen throughout the entire duration of the trial and so the time-zero of the ERPs and GBR was set to be at the end of a saccade (fixation onset). Hence the interval between fixation and the time the visual information reaches the primary visual cortices might be shorter than the interval between stimulus onset and primary visual activity in a classical central fixation paradigm. However, further investigations will be needed to validate these interpretations.

Statistical Considerations for iEEG Data Analysis and Interpretations

Intracranial EEG data analysis is complicated by the fact that populations are often small, and the recording sites are highly variable across patients. As a consequence, group statistics, as they are commonly used in MEG/EEG studies, are not suitable to many iEEG studies. Instead, task-related effects can be shown at the individual level and localized precisely on the cortical anatomy of each patient. The attempt to represent statistically significant task-related modulations of iEEG data across subjects,

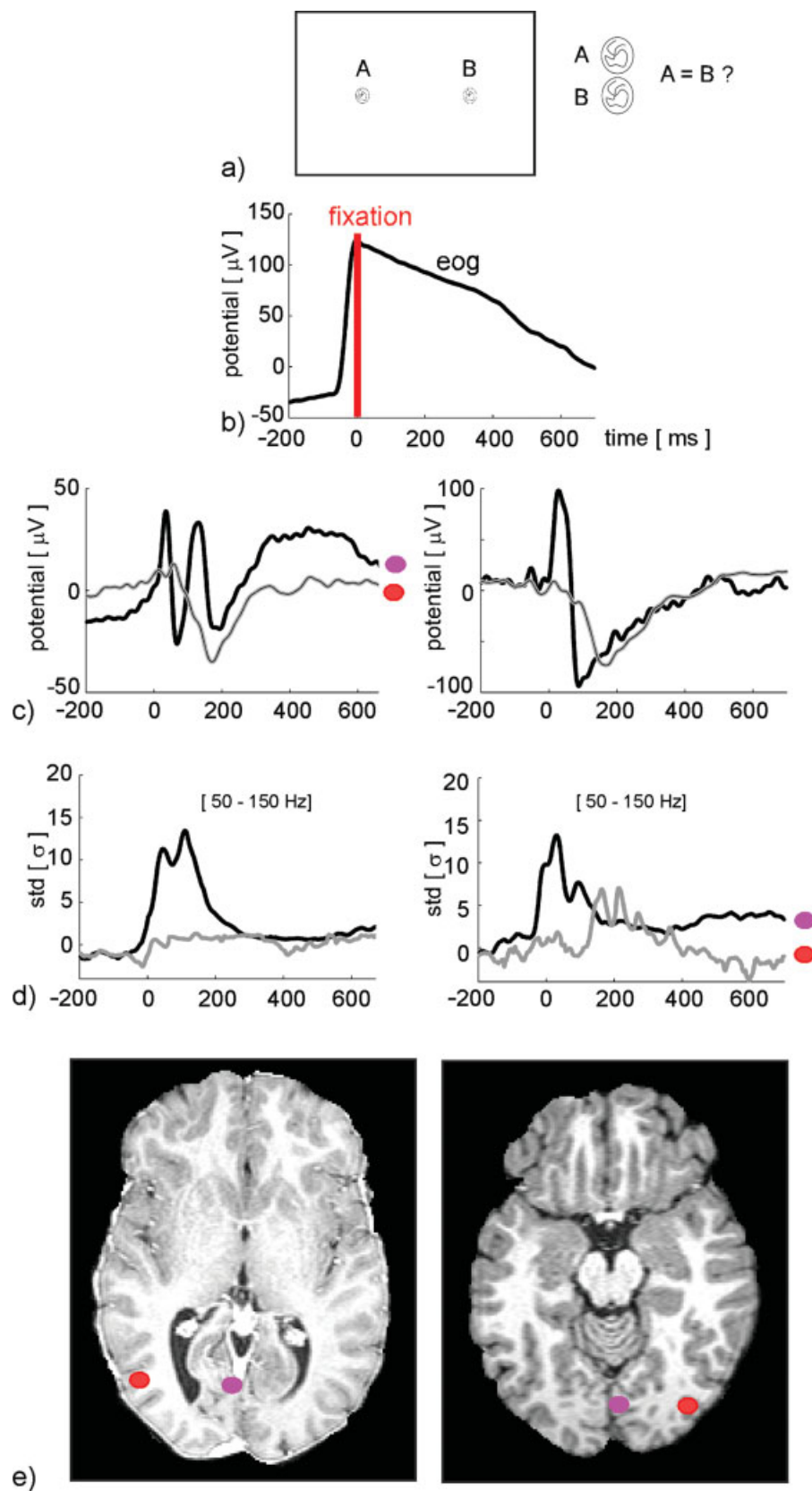


Figure 4.

Example study. Free viewing in human early visual areas. **(a)** Schematic representation of the behavioral task. Stimuli were separated from each other by 10 degrees, centered on the middle of the screen, and had a diameter of 1 degree. Both stimuli were present during the entire trial, which was ended by a behavioral response of "same" or "different" made through a computer mouse. **(b)** Electroculogram (EOG) recording showing the method used to determine the end of a saccade (fixation onset). **(c)** ERPs and **(d)** GBRs as recorded in two electrodes for two patients. Black and gray traces represent the activation recorded from primary visual and latero-occipital areas. Left and right panels correspond to patient one and two. **(e)** Magnetic resonance images of a horizontal cut from brains of each patient. Red and magenta dots show the location of the electrode contacts.

time, space and frequency is in itself quite a unique neuro-imaging challenge. One approach used in our group to deal with this complexity consists of the following three-step procedure: First, a statistical comparison is performed between experimental conditions at the individual level, on each recording site, to identify regions of interest with task-related neural responses. This includes a correction for multiple comparisons and may involve either a direct comparison between two conditions or a comparison between the task and a pre-stimulus resting baseline. The second step is the identification of brain regions of interest which show similar effects across several patients. The third step is to display the individual data for each region of interest, displaying the task-related effect on each patient's anatomical MRI. The above steps are illustrated in Supporting Information Figure 1. Such a procedure has proven to be particularly well-suited for analyzing depth-electrode recordings in populations of ten to twenty patients [Jung et al., 2008; Mainy et al., 2007].

ONLINE MONITORING OF INTRACRANIAL OSCILLATORY ACTIVITY (BRAIN TV)

In a recent implementation, we proposed an iEEG real-time system that computes and displays the variations of ongoing alpha, beta and gamma-band activations at each recording site [Lachaux et al., 2007a]. The system, dubbed *Brain TV*, allows the experimenter, clinical staff as well as the patient to visualize the immediate effect of his behavior on brain oscillations. As an example, while monitoring iEEG activity in the superior temporal gyrus in one patient with the real-time system, a selective reactivity of the gamma activity to certain aspects of speech perception was suspected (such as perceiving a change of speaker). The hypothesis was then confirmed and fine-tuned using follow-up experiments tailor-designed to probe the observed phenomenon [Lachaux et al., 2007a]. A similar approach has also been used to map the motor cortex [Miller et al., 2007]. More importantly, the *Brain TV* set-up holds the potential of revealing previously unsuspected correlations between various mental events and the online display of oscillatory activity. Such events may also be covert cognitive operations and part of the patient's subjective experience.

Figure 5 shows an illustrative example of the application of the *Brain TV* platform. While monitoring the power of ongoing alpha oscillations measured by one specific electrode, the patient reported that a decrease in the displayed activity appeared to be associated with vision, in particular to focused vision. The monitored electrode position turned out to be in the superior parietal lobule (SPL, BA 7) and when cued to switch between a visual attention state and an auditory attention state systematic alternations between alpha suppression and enhancement were visible on the *Brain TV* set-up (Fig. 5b). These qualitative online observations provide single-trial evidence that alpha modulations in the SPL are modulated by visual attention.

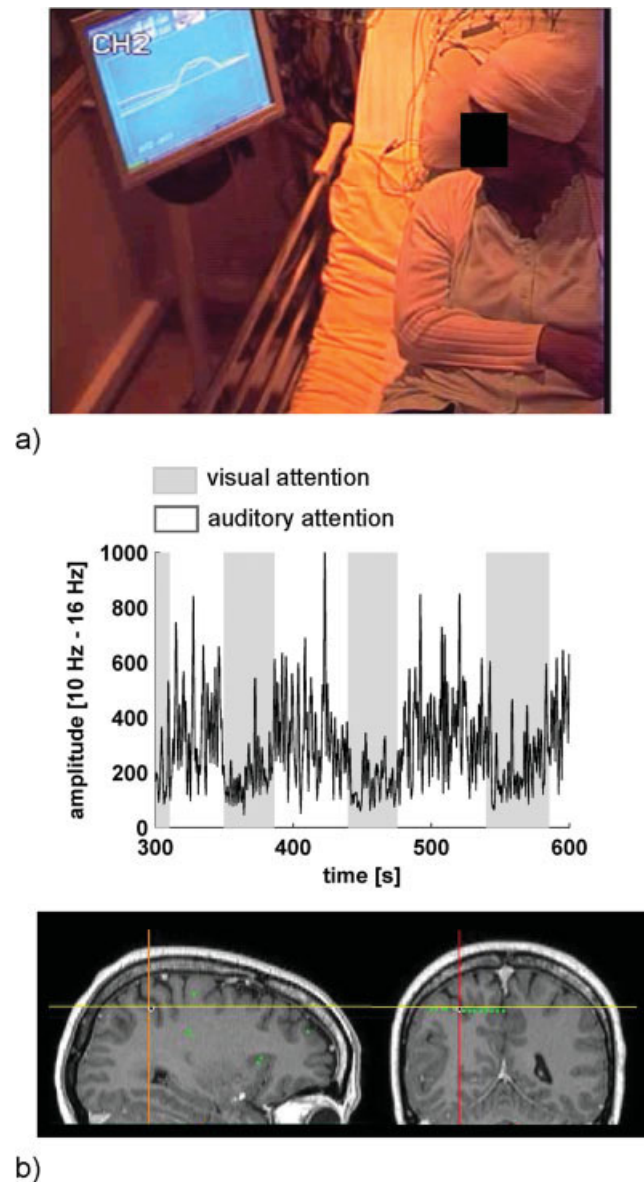


Figure 5.

Online measurements of visual attention with *Brain TV*. (a) The *Brain TV* set-up allows patients to visualize ongoing alpha, beta or gamma-band activity measured in real-time in specific regions of their brain. (b) Using the set-up, one patient was able to achieve online control of the activity recorded in her superior parietal lobe within the 10-16 Hz frequency range. She reported her ability to modulate the activity by focusing her attention on distant visual objects. The subject was then cued to switch between auditory and visual attention. The graph depicts the online variations of the activity as she shifted her attention back and forth between vision (in gray) and audition (in white). These online observations of alpha ERD during visual attention are inline with previous offline studies.

Beyond investigating the functional role of neural oscillations, the online system also has immediate applications as a clinical tool for pre-surgical mapping (as a complement to electrocortical stimulation) [Lachaux et al., 2007a] and can be directly used in explorative investigations for the development of novel brain computer interface (BCI) strategies [Jerbi et al., 2007, in press].

IMPLICATIONS FOR MEG AND EEG

Invasive EEG recordings are restricted to a number of clinical conditions that require the surgical implantation of intracerebral recordings. Therefore, while it is fortunate that access to such data is sometimes possible for research purposes, it is clearly an exceptional setting. It is therefore important to ask whether the findings obtained via access to such fine-scale recordings in humans has implications on investigations based on non-invasive electrophysiological techniques such as MEG and scalp-EEG. Indeed, findings of iEEG would almost invariably benefit from a validation in a large population of healthy subjects. Of course, this assumes that the phenomena reported invasively can also be detected using non-invasive techniques. In particular, it is unclear to which extent the growing body of evidence on high gamma activity (60–200 Hz) reported with iEEG can be replicated using EEG and MEG. The detection of gamma-band activity in EEG and MEG signals is complicated by several factors related in one way or another to a low SNR at this high frequency range. EEG and MEG sensors inherently measure the summed activity from multiple neural populations. While the skull is assumed to have similar impedance at both low and high frequencies, active patches of cortex can exhibit large phase variability, and the resulting polyphasic summation effectively results in lowpass filtering [Pfurtscheller and Cooper, 1975]. As discussed above, the spatial extent of oscillatory power modulations in the high gamma range is generally more focal than in the lower alpha and beta frequencies [Crone et al. 1998a; Edwards et al. 2005], which implies less signal reaches the scalp since the active patch may be relatively small. A further issue that limits the detectability of high gamma activity is the presence of artifacts. EEG and MEG signals can be contaminated by EMG signals from oculomotor and head muscles with spectral characteristics similar to that of physiological gamma-band activity [Yuval-Greenberg et al., 2008].

Despite these limitations, several studies have reported gamma-band activity using MEG or EEG in a variety of experimental conditions, including motor [Ball et al., 2008; Cheyne et al., 2008; Dalal et al., 2008b; de Lange et al., 2008; Gonzalez et al., 2006; Pfurtscheller et al., 1993; Salenius et al., 1996], oculomotor [Jerbi et al., 2008; Medendorp et al., 2007; Van der Werf et al., 2008], sensory [Hoogenboom et al., 2006; Tecchio et al., 2008], visual [Chaumon et al., 2008; Muthukumaraswamy and Singh, 2008a; Rodriguez et al., 1999; Tanji et al., 2005] behavior as well as in decision making [Guggisberg et al., 2007]

pain [Gross et al., 2007] and attention [Schurger et al., 2008; Vidal et al., 2006] processes.

In general, the increasing number of reports of widely distributed networks of high gamma activity detected with iEEG in various experiments and across numerous structures suggests that increasing sensitivity to high frequency oscillations might be a priority for future research with non-invasive techniques. This may be achieved by optimizing three distinct aspects of non-invasive studies: (1) Adapted experimental design: one way to compensate for the low SNR of high gamma activity is to ensure a large number of trials (e.g., 200 trials or more) per condition. In addition, the design should be carefully adapted to the source estimation procedure that will be subsequently used. This might involve ensuring sufficiently long epochs to improve the estimation of signal and noise covariance. Furthermore, block design experiments, if suitable to the investigated question, might help drive the neural networks into a sustained activation state, which could positively affect the SNR, compared to that associated with transient neural phenomena. (2) Improving artifact detection and rejection: As discussed above, disambiguating physiological and artifactual gamma range activity is a non-negligible concern. This can be enhanced by systematic and accurate monitoring of the possible source of artifact. Electromyograms and electrooculograms (EOG) should be used systematically and the respective traces should be used both for visual inspection and automatic or semi-automatic artifact detection. Independent component analysis may also be used for artifact removal. Furthermore, in the light of recent concerns linking miniature saccades and gamma components of the EEG [Yuval-Greenberg et al., 2008], accurate monitoring of eye movements using dedicated eye-tracking systems might become critical for future studies. Note however, that although this issue might be of direct relevance to scalp-EEG studies, it may be less critical issue for MEG which is reference-free. Indeed the artifact was shown to be prominent for nose-referenced EEG data which re-injects the microsaccadic activity into distant occipital electrodes. Nevertheless, the susceptibility of MEG to contamination by microsaccade artifacts requires further investigation. As a matter of fact, we have recently shown that even iEEG, which is predominantly immune to saccade artefacts, can display artifactual gamma power increases at depth electrodes located close to the extra-ocular eye muscles [Jerbi et al., 2009]. (3) Using source reconstructions: source reconstruction techniques may potentially prove to be crucial for the detection of task-related high gamma activity that is not readily detectable at the sensor level. Source estimation based on minimum norm solutions or on beamforming have successfully been used in the past to detect high gamma (>60 Hz) activity in MEG data [Cheyne et al., 2008; Dalal et al., 2008b; Van Der Werf et al., 2008]. Insights into optimizing source estimation techniques to increase sensitivity to high gamma activity will definitely benefit from recent studies of simultaneous acquisitions of iEEG and MEG recordings

in the same patient (Dalal et al., in press; Lachaux et al., 2007c]. Moreover, source estimation of such high frequency activity may also be improved by the use of data from iEEG as a source of a priori constraints for EEG/MEG source analysis. Additionally, granted that future studies firmly establish that BOLD and gamma-band activity are indeed tightly linked, then fMRI studies could also be used to provide a priori knowledge of the origin of gamma-band responses and be used for EEG/MEG source localization. Finally, investigating the correspondence between lower frequency findings in invasive and non-invasive recordings is equally crucial. For instance, the discrepancy between the spatial and functional specificity of alpha versus beta motor rhythms reported in MEG [Salmein et al., 1995] and the lack thereof in some iEEG studies will have to be resolved.

CONCLUSION

Albeit being sometimes faced with a fair share of skepticism or, at times, with excessive fascinations, intracranial recordings in humans has grown into a field of its own providing a steady stream of novel observations that have advanced our understanding of brain function. Intracerebral recordings, especially of gamma activity, may play a pivotal role in providing a means to better understand the links to data reported in animal electrophysiology and to findings of neuroimaging studies. In addition, advances in non-invasive electrophysiological recordings will be key to validating and possibly extending findings of invasive studies. Future trends include increased direct sampling of single-unit neural activity in the human brain via various microelectrode recording techniques [Neves and Ruther, 2007; Ulbert et al., 2001]. Combining microelectrode data and population level recordings will be crucial in order to elucidate the neural mechanisms that encode information processing and communication within local and large-scale cerebral networks. This said, the increasing scientific appeal of invasive human recordings will also have to be associated with enhanced vigilance to questions of ethics and patient safety.

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